# The Central Nucleus of the Amygdala is a Critical Substrate for Individual Differences in Anxiety

Jonathan A. Oler [1,2], Andrew S. Fox [1,2], Alexander J. Shackman [3] and Ned H. Kalin [1,2]

1. Department of Psychiatry
   University of Wisconsin School of Medicine and Public Health
   6001 Research Park Boulevard, Madison, Wisconsin 53719 USA

2. HealthEmotions Research Institute
   University of Wisconsin-Madison
   Madison, Wisconsin 53719 USA

3. Department of Psychology
   Neuroscience and Cognitive Science Program, and the Maryland Neuroimaging Center
   University of Maryland, College Park
   3123G Biology-Psychology, College Park, Maryland 20742 USA

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Research into the function of the amygdala began with experiments in rhesus monkeys, performed by Brown and Schaefer (Brown and Schafer, 1888) and later by Klüver and Bucy (Klüver and Bucy, 1937; Klüver and Bucy, 1939). These studies led to further critical experiments in nonhuman primates that continued to specify the amygdala's role in emotion and social behavior (Weiskrantz, 1956; Kling, 1968; Kapp et al., 1979; Pribram et al., 1979; Aggleton and Passingham, 1981; Rolls, 1984; Zola-Morgan et al., 1991). Advances in lesion techniques and other invasive and non-invasive methodologies have motivated more nuanced hypotheses regarding the adaptive role of the amygdala in fear, danger detection, social behavior, vigilance, and temperament (Kalin, 1997; Whalen, 1998; LeDoux, 2000; Adolphs, 2003; Amaral, 2003). There is now great interest in understanding alterations in amygdala function in relation to psychopathology, with a particular emphasis on anxiety and affective disorders.

Understanding the role of the amygdala in anxiety and affective disorders is essential because these disorders are among the most common psychiatric illnesses in youth and adults (33.7% lifetime incidence of any anxiety disorder; 18.3% lifetime incidence of major depressive disorder), and they are highly comorbid and often resistant to treatment (Kessler et al., 2012). Anxiety disorders frequently begin during the preadolescent years and in many cases are associated with the later onset of depression during adolescence and early adulthood. Research demonstrates that very young children with extreme anxiety, as manifested by marked reactivity to novelty and/or strangers, are at increased risk to develop anxiety and affective disorders. For example, extreme temperamental childhood anxiety is a strong predictor of the later development of social anxiety disorder (Schwartz et al., 1999; Prior et al., 2000; Biederman et al., 2001; Hirshfeld-Becker et al., 2007; Chronis-Tuscano et al., 2009; Essex et al., 2010), and depressive disorders (Caspi et al., 1996; Gladstone and Parker, 2006; Beesdo et al., 2007). A recent meta-analysis supports the contention that extreme childhood temperamental anxiety may represent the single best predictor of the later development of social anxiety disorder (Clauss and Blackford, 2012). Appreciating why certain individuals are vulnerable to developing anxiety disorders requires an understanding of the neural mechanisms that influence the development of adaptive anxiety, as well as extreme temperamental anxiety (Yehuda and LeDoux, 2007; McEwen et al., 2012; Galatzer-Levy et al., 2013; Goswami et al., 2013; Grupe and Nitschke, 2013; Holmes and Singewald, 2013; Shackman et al., 2013).

Our ultimate goal is to provide insight into the developmental issues related to the onset of mood and anxiety disorders. Therefore, we have focused our efforts on understanding the developmental pathophysiology of these illnesses by studying the role of the amygdala early in the life of primates as it relates to the initial manifestations of extreme anxiety. Our studies in young rhesus monkeys suggest that the central nucleus of the amygdala (Ce) and the bed nucleus of the stria terminalis (BST; part of the extended amygdala), are key substrates for trait-like differences in anxiety. The Ce is often conceptualized as the major output structure of the amygdala for projections to the brain stem and hypothalamus, and the Ce is thought to coordinate and gate the physiological and behavioral effects of fear (Davis, 2000; Pare et al., 2004; Ciocchi et al., 2010; Haubensak et al., 2010). Additional hypotheses of Ce function have been postulated to account for its role in appetitive learning and attention (Kapp et al., 1992; Gallagher and Holland, 1994; Gallagher, 2000; Everitt et al., 2003; Gabriel et al., 2003). The Ce is also conceptualized as the temporal lobe component of the 'central extended amygdala', a hypothesized macrostructual anatomic entity that extends into the basal forebrain (Alheid and Heimer, 1988; de Olmos and Heimer, 1999; Heimer and Van Hoesen, 2006). The basal forebrain is a complex region that has only recently become accessible to study in the living primate. Because of its strategic location and putative functions, dysfunction of the basal forebrain has been implicated in various neuropsychiatric disorders (Heimer, 2003). The major components of the basal forebrain, including the cholinergic nucleus basalis of Mynert, the ventral striatopallidal system and the extended amygdala, are highly interdigitated making it challenging to elucidate selective functions of these basal forebrain components (Zaborszky et al., 2008). The central extended amygdala concept proposed by Heimer and colleagues to describe the continuum of GABA-ergic neurons that run from Ce, through the substantia innominata, to BST and the shell of the nucleus accumbens complements the other models of Ce function mentioned above. In addition to being highly interconnected, the Ce and BST share many of the same efferent targets, reinforcing the idea that Ce and BST together form a coherent functional unit (de Olmos and Heimer, 1999). Consistent with these anatomical and neurochemical findings, functional MRI (fMRI) data from our laboratory demonstrate that in monkeys and humans the Ce and BST display highly significant functional connectivity at rest or under anesthesia, supporting the hypothesis that these structures form a discrete circuit (Oler et al., 2012). An alternative view, however, considers the Ce, sublenticular substantia innominata and BST continuum as

differentiated components of a striatopallidal projection system (Dong et al., 2001; Swanson, 2003).

Rodent studies suggest an important dissociation between subdivisions of the Ce and the BST with respect to defensive behaviors, such that the medial division of the Ce (CeM) is involved in rapid, phasic fear-related responding, whereas the BST via inputs from the lateral division of the Ce (CeL) is thought to mediate slower, sustained anxiety-like responses to diffuse or ambiguous threats (Walker and Davis, 2008). Additionally, recent human imaging studies have associated the BST region with vigilance, threat monitoring and anticipatory anxiety (Straube et al., 2007; Alvarez et al., 2010; Mobbs et al., 2010; Somerville et al., 2010; Choi et al., 2013; Grupe et al., 2013; Avery et al., 2014), and some evidence for a Ce and BST functional dissociation, similar to that in rodents, has been reported in humans (Davis et al., 2010).

Here we review studies from rhesus monkeys aimed at understanding the role of the amygdala in temperamental anxiety, and provide evidence demonstrating that the central extended amygdala plays a critical role in early-life anxiety. We first recount the development and validation of the non-human primate model of childhood anxiety. Next, we discuss neuroimaging and genetic evidence from the rhesus monkey showing that the anxious phenotype, or anxious temperament, is heritable and strongly related to individual differences in Ce function. We then describe evidence from mechanistic studies demonstrating that behavioral expression of primate anxiety critically depends upon the integrity of the Ce. We conclude by outlining the implications of these findings for understanding the risk for anxiety-related psychopathology, for potentially developing more effective early-life interventions, and for understanding normal variation in childhood temperament.

## Developing the Human Intruder Paradigm and the Concept of Anxious Temperament

From our nonhuman primate studies, we developed the term anxious temperament (AT) to describe an individual's underlying predisposition to display extreme anxiety-related behavioral and physiological responses early in life. There is considerable evidence that the amygdala plays a critical role in normal fear and emotional processing (Aggleton, 1992; Aggleton, 2000; Shinnick-Gallagher et al., 2003), altered amygdala function has been reported in adults with anxiety disorders (Etkin and Wager, 2007) and administration of clinically effective anxiolytics reduces amygdala activation in a dose-dependent manner (Paulus et al., 2005). In addition, adults with a history of childhood AT display increased amygdala reactivity to novel or

potentially fearful stimuli (Schwartz et al., 2003; Blackford and Pine, 2012). However, the amygdala's contribution to early life presentation of trait-like individual differences in childhood anxiety remains unclear. Specifying the processes within the amygdala that underlie the development of normal and abnormal anxiety will be essential for developing novel neuroscientifically-grounded interventions for treating and preventing anxiety-related psychopathology.

The behavioral assay for monkeys developed by Kalin and Shelton termed 'the human intruder paradigm' was conceptualized, in part, to map onto studies characterizing behavioral inhibition in human children. The human intruder paradigm consists of three different consecutively presented conditions (Alone, No-Eye-Contact, and Stare) that elicit different, contextually appropriate, anxiety-related defensive responses (Kalin and Shelton, 1989); see Figure 1). In the 'Alone' condition, animals are separated from their cage-mates and placed by themselves in a novel test cage. During the 'No-Eye-Contact' (NEC) condition, which follows the Alone condition, a human intruder enters the room and at 2.5 meters from the cage presents his/her profile to the monkey. The critical component of this condition is the lack of eye contact between the human intruder and the test monkey. While eye contact signals a direct threat, the avoidance of eye contact provides a different potentially threatening context. The intruder then leaves the room for a brief period. Upon reentering, the 'Stare' condition ensues, during which the intruder continuously stares at the monkey with a neutral facial expression (Kalin, 1997).

[insert Figure 1 here]

A number of standardized behavioral paradigms exist to measure childhood behavioral inhibition (Fox et al., 2005). These paradigms include the introduction of a stranger to the room with a young child (Buss et al., 2004), and exposure of a child to novel objects and social situations (Kagan et al., 1988). Individual differences in physiological responses to stress have also been examined in relation to behavioral inhibition. Many of these studies have focused on pituitary-adrenal activity and report mixed results. Initial studies demonstrated associations between cortisol and behavioral inhibition in children, or between cortisol and AT in monkeys (Kalin et al., 1998; Essex et al., 2002), however later studies did not consistently replicate these findings (Shackman et al., 2013). While not as extensively studied, evidence points to an

association between heart rate and right frontal EEG asymmetry with extreme childhood BI and monkey AT (Davidson et al., 1992; Davidson et al., 1993; Kalin et al., 1998; Fox et al., 2005).

Our definition of AT parallels the construct of behavioral inhibition used by Kagan and colleagues in their description of extremely shy toddlers that were observed to become immobile and hesitant to vocalize in the face of potential threat (Kagan et al., 1988). Freezing behavior in response to the NEC condition of the human intruder paradigm, because of its obvious similarity to human behavioral inhibition, was the initial metric used to assess threat-related anxiety in young monkeys (Kalin and Shelton, 1989; Kalin and Shelton, 2000; Kalin and Shelton, 2003; Kalin et al., 2005). As a validation of its relevance to anxiety, we demonstrated that NEC-induced freezing in monkeys can be reduced by administration of the benzodiazepine, diazepam, a common pharmacological treatment for clinically significant anxiety (Kalin and Shelton, 1989; Davidson et al., 1993; Kalin, 2003), and increased with administration of ß-carboline, an anxiogenic benzodiazepine inverse agonist (Kalin et al., 1992). We later expanded the assessment of monkey anxiety to move beyond just a single behavioral measure (i.e., freezing) to a composite measure, by including decreases in spontaneous coo-calls (Fox et al., 2005) as well as individual differences in threat-induced cortisol levels (Jahn et al., 2010). This was, in part, based on the observation that animals with elevated freezing in response to the NEC condition concomitantly emitted fewer vocalizations (Kalin and Shelton, 1989). Threat-induced cortisol was added to gauge individual differences in pituitary-adrenal reactivity (Kalin and Shelton, 1989; Kalin et al., 1998). It is important to note, that when examining the relations among the three components of AT (freezing, reduced cooing and cortisol levels) in a large sample, individual differences in cortisol levels do not significantly correlate with either behavioral metric, whereas freezing and cooing are moderately inversely correlated (Shackman et al., 2013). The inclusion of cortisol in the composite measure of AT is intended to capture the heterogeneity in individual differences in the physiological response to fear and anxiety eliciting stimuli. Interestingly, the AT composite better predicts individual differences in amygdala metabolism than any one of its three components (Fox et al., 2008; Shackman et al., 2013).

To be clear, we specifically use the term AT to operationalize the theoretical construct representing an individual's disposition to behave with reticence and respond to potential threat with extreme behavioral and physiological reactivity. Our definition of AT includes behavioral inhibition (i.e., freezing and decreased spontaneous vocalization), but also takes into account the degree of pituitary-adrenal stress-responsiveness of the individual (see Figure 2a).

Table 1 demonstrates the translational utility of AT as a model for childhood behavioral inhibition or the early childhood risk for developing social anxiety. As mentioned above, it is well documented that highly anxious children are at substantial risk for social anxiety disorder (SAD). The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) lists the following as criteria for SAD diagnosis, many features of which are shared by both childhood behavioral inhibition and monkey AT (italics added): SAD Criterion A: Marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions (e.g., meeting *unfamiliar people*), being observed, and performing in front of others. Criterion B: The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated. Criterion C: The social situations almost always provoke fear or anxiety. **Note**: In children, the fear or anxiety may be expressed by crying, tantrums, *freezing*, clinging, shrinking, *or failing to speak in social situations*. Criterion D: The social situations are avoided or endured with intense fear or anxiety. Criterion E: The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context. Criterion F: The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more. Criterion G: The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. Criterion H: The fear, anxiety, or avoidance is not attributable to the physiological effects of a substance or another medical condition. Criterion I: The fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder. Criterion J: If another medical condition is present, the fear, anxiety, or avoidance is clearly unrelated or is excessive (American Psychiatric Association, 2013). As shown in Table 1, the AT phenotype in young monkeys and the behaviorally inhibited phenotype in young children share a number of common features. Many of these common features are antecedents of SAD. We believe that extreme AT in children, when stable and trait-like, has the hallmarks of sub-threshold SAD but is not severe enough to satisfy the functional impairment criterion.

[insert table 1 here]

**Neuroimaging studies link individual differences in Ce function to anxiety**

Our initial $^{18}$F-fluorodeoxyglucose (FDG) - positron emission tomography (PET) imaging studies demonstrated that monkey AT was correlated with metabolism in the amygdala and the

extended amygdala (i.e., BST), as well as anterior hippocampus, anterior temporal lobe, and periaqueductal grey (PAG) (Fox et al., 2005; Kalin et al., 2005). FDG is a radiolabeled glucose analog with a half-life of ~110 minutes that does not get metabolized and remains trapped in metabolically active cells (Sokoloff et al., 1977). Because the time course of FDG uptake reflects brain activity over an approximate 30-minute period, and remains stably detectable in the brain, it is an ideal radiotracer to simultaneously study behavior and brain activity elicited by exposure to ethologically-relevant situations (see Figure 2b). FDG-PET is therefore particularly useful in understanding the sustained brain responses associated with temperament, which by definition is a persistent and relatively context-independent emotional disposition.

[insert Figure 2 here]

We performed FDG-PET scans on animals exposed to 4 different conditions, 2 of which were stressful (NEC and Alone-separation from cage-mate into a test-cage) and 2 of which were nonstressful (in home-cage without cage-mate, and in home-cage with cage-mate). Our findings revealed consistent positive correlations between individual differences in NEC-elicited AT with metabolism in the amygdala, hippocampus, anterior temporal pole, and PAG regardless of the stressful or nonstressful condition in which brain metabolic activity was assessed (Fox et al., 2008). Remarkably, the AT brain metabolism phenotype was discernible in the absence of provocation, when monkeys were at home with their cage-mate, something that is virtually impossible to measure in humans. These results suggest that the neural correlates of AT are stable across contexts and not as context-dependent as the observable behavioral and pituitary-adrenal responses associated with AT. Similarly, we examined the stability of AT's neural substrates across time by assessing FDG-PET and AT in response to NEC in 24 animals 3-times over the course of 6-18 months (Fox et al., 2012). Results demonstrated that brain metabolism within AT-related regions was stable over time, and mean brain metabolism (across the 3 assessments) predicted mean AT (Fox et al., 2012). Collectively, these data indicate that the trait-like nature of AT is reflected by context-independent and temporally stable neural substrates that are instantiated in the inherent activity of an individual's brain.

To further explore the neural substrate underlying AT and to elucidate the heritable basis of AT, we performed an experiment examining FDG-PET and AT in response to the NEC context in a large sample (n = 238) of young rhesus monkeys (Oler et al., 2010). Because of the statistical

power afforded by the large sample size, we used extremely stringent statistical thresholds (Šidák corrected), which increases confidence in the findings. Consistent with earlier findings, the imaging data demonstrated that metabolism in anterior temporal lobe structures including the Ce region, anterior hippocampus and anterior temporal cortex predicted individual differences in AT (Figure 3).

[insert Figure 3 here]

At the Šidák threshold ($p = 0.00000005875$), large bilateral anterior temporal lobe clusters that correlated positively with AT were observed (Oler et al., 2010). The anterior temporal lobe clusters contained multiple spatial peaks, each of which correlated with AT. Therefore, we further resolved the location of the peak correlations within the anterior temporal lobe clusters by calculating the spatial confidence intervals representing volumes that with 95% certainty contained the peak correlations between metabolic activity and AT (see Oler et al., 2010 for details). To further demarcate and define the location of these peaks, we used *in vivo* chemoarchitectonic techniques to demonstrate that this functionally-defined region corresponds to the Ce, a degree of precision that is difficult to achieve using conventional imaging techniques in humans. The volumes contained within the 95% confidence intervals were superimposed on a voxelwise map of serotonin transporter (5-HTT) binding created from an independent sample of rhesus monkeys assessed with $^{11}$C-DASB PET (Christian et al., 2009; Oler et al., 2009). This 5-HTT map (see Figure 4) can be used to localize the Ce and differentiate it from the anterior hippocampus, since compared to surrounding regions the lateral division of the Ce (CeL) has the highest density of 5-HTT binding (O'Rourke and Fudge, 2006).

[insert Figure 4 here]

**Demonstrating heritability of AT and initial studies of the genetic basis of AT**

To ascertain whether individual differences in AT are heritable, we took advantage of the fact that the young rhesus monkeys in the study all belong to a single multigenerational pedigree of more than 1,800 individuals. The power of the extended pedigree approach to quantitative genetic analysis stems from the many closely related, distantly related and unrelated pairs of individuals that all contribute information about the effects of shared genes on phenotypic

similarity. Specifically, among the monkeys with phenotype data and confirmed lineage, there were three full-sibling pairs, 189 half-sibling pairs, 128 third-degree relative pairs, 372 fourth-degree relative pairs, and much larger numbers of more distantly related and unrelated pairs. Using a general variance components method (Almasy and Blangero, 1998), we estimated the heritability of AT while including covariates such as sex, age, and their interactions in the mean effects model to control for extraneous sources of variance (for methodological details see supplemental materials from Oler et al., 2010). Consistent with previous reports in rhesus monkeys (Williamson et al., 2003; Rogers et al., 2008), and the genetic epidemiology of human anxiety disorders (Hettema et al., 2001), approximately 36% of the variability in AT was accounted for by the pair-wise relationships among the animals.

We used this same quantitative genetic approach to estimate the heritability of metabolic activity at each voxel where FDG metabolism significantly predicted differences in the anxious phenotype (see Figure 5). Remarkably, although glucose metabolism in the Ce and anterior hippocampal peak regions were similarly predicative of AT, these regions were differentially heritable. Unlike Ce metabolism, anterior hippocampal metabolism was significantly heritable and this level of heritability was significantly greater than the heritability estimate for the Ce (Oler et al., 2010). We interpreted these findings cautiously as even this large sample size is relatively modest for tests of additive genetic effects, but the results suggest that the Ce may be particularly influenced by the environment and experience, and set the stage for further experiments aimed at understanding the neurodevelopmental origins or AT. These results also highlight the important observation that it is possible to dissociate heritable from non-heritable neural substrates - something that, to our knowledge, has never been shown in prior work.

[insert Figure 5 here]

At a more specific level, we examined DNA variation in candidate genes as they relate to AT and its underlying amygdalar and hippocampal metabolism. We selected the serotonin transporter-linked polymorphic region (5-HTTLPR) because variation in this gene was shown by numerous groups to predict fear-related behaviors and the risk for affective disorders (Hariri and Holmes, 2006). The effects of the 5-HTTLPR genotype on the risk to develop anxiety are not straightforward, and may only be revealed when examining brain reactivity, for example when comparing stressful and non-stressful conditions or, as is required in the analysis of fMRI data, a

change from baseline. We observed no effect of the 5-HTTLPR promoter repeat length polymorphism on AT or AT-related glucose metabolism (Oler et al., 2010). This was not surprising considering that 1) a large imaging study using arterial spin labeling found no effect of 5-HTTLPR genotype on baseline amygdala blood flow (Viviani et al., 2010), and 2) a previous study in a smaller sample of monkeys failed to observe 5-HTTLPR genotype-related differences in NEC-induced FDG (Kalin et al., 2008). Kalin et al., (2008) did, however, find 5-HTTLPR genotype-related alterations when comparing the *difference* in metabolism between the NEC condition and a "safe" condition, where the animals were administered FDG in their home cages. In contrast to the AT findings, these data demonstrate an association between context-dependent metabolic changes and the 5-HTTLPR genotype. Interestingly, in the same sample of monkeys the 5-HTTLPR genotype was not significantly associated with $^{11}$C-DASB binding, a measure of 5-HT transporter availability (Christian et al., 2009). Collectively, these findings highlight the complexity of the influence that the 5-HTTLPR, and other functional polymorphisms, have on behavior and the risk for psychopathology, and support the idea that neurogenetics research should focus on gene  environment interactions (Caspi et al., 2010; Hyde et al., 2011; Bogdan et al., 2013).

In contrast to the short and long allelic variation in the 5-HTTLPR, single nucleotide polymorphisms (SNPs) in the corticotropin releasing hormone receptor 1 (CRHR1) gene, which has been associated with risk for the development of anxiety-related disorders (Bradley et al., 2008), were significantly associated with both AT and AT-related glucose metabolism. Specifically, SNPs in exon 6 of the rhesus CRHR1 gene appear to confer an increased likelihood of elevated AT and greater NEC-related metabolism in the Ce and anterior hippocampus (Rogers et al., 2013). This finding is particularly interesting because exon 6 is found primarily in anthropoid primates. Much of the human CRHR1 genetic data report gene  environment interactions, especially interactions with early childhood trauma (Bradley et al., 2008). Thus, these findings suggest that the early-life effects of CRHR1 genetic variation may be to support the development of a diathesis that interacts with early adversity to increase the likelihood of developing pathological anxiety.

**Molecular substrates within the Ce relevant to AT**

As anxiety and affective disorders can be resistant to current treatments, and these treatments are commonly associated with significant adverse effects (Bystritsky, 2006; Cloos and

Ferreira, 2009; Kessler et al., 2012) there is great need for identifying new anxiolytic and antidepressant molecular targets. Furthermore, because of the early-life onset of anxiety, establishing novel early-life interventions aimed at preventing chronic and debilitating outcomes would be an ideal treatment approach. To develop novel interventions for anxiety disorders, it is necessary to identify potential treatment targets and to test their therapeutic feasibility in a species that expresses anxiety-related psychopathology that is similar to human symptomatology. In this regard, quantitative mRNA approaches are particularly useful because they capture the combined impact of genetic and environmental epigenetic regulation (Jaenisch and Bird, 2003). With microarray or deep RNA sequencing data we can identify individual differences in mRNA expression levels of specific genes that predict AT and altered metabolism within the AT neural circuit (Fox et al., 2012; Roseboom et al., 2013).

The monkey model of childhood AT allows us to dovetail the same multimodal imaging methods routinely used in humans with in depth post-mortem brain molecular analyses. Our initial approach has been to collect brain tissue punches from a subset of monkeys phenotyped for AT. Using the imaging data as a guide, from the brains of 24 male monkeys we selectively biopsied the region of the dorsal amygdala where its metabolism was most predictive of AT (Figure 6). Affymetrix rhesus microarray chips were used to assess mRNA expression that was analyzed in relation to individual differences in AT and Ce metabolism (see Figure 6). Analyses controlling for housing differences, hemisphere sampled, and age revealed that AT was associated with a number of mRNAs that had at least moderate expression levels [>log2(100)], and remained significantly correlated with AT after correcting for multiple comparisons (FDR $q < 0.05$, two-tailed; see Fox et al 2012 for detailed methods). A gene ontology enrichment analysis of all the significant AT-related mRNAs revealed that expression levels of gene families associated with neuroplasticity and neurodevelopment significantly predicted differences in AT (Fox et al., 2012). Specifically, this transcriptome-wide analysis revealed that AT and increased Ce metabolism was associated with decreased expression levels of several genes in the NTF-3 (neurotrophin-3)-NTRK3 pathway (see Figure 6). NTRK3 (neurotrophic tyrosine kinase receptor-3, also termed TrkC) is of considerable interest because its activation can initiate synaptogenesis and neurogenesis (Bernd, 2008). In addition, NTRK3 genetic variation has been linked to human psychopathology (Otnaess et al., 2009) and because the NTRK3 protein is a cell surface receptor, NTRK3 may provide an accessible drug target. These unique findings in a primate species suggest that the expression and maintenance of AT and the subsequent

increased risk to develop anxiety and depression may be due to early maladaptive neurodevelopmental processes (Fox et al., 2012).

[insert Figure 6 here]

The findings from the microarray experiment also demonstrated that Ce metabolism and AT were associated with altered expression of some expected candidates genes (e.g., 5HT2C and NPY1R). Levels of mRNAs for both of these genes were negatively correlated with AT, such that individuals with the lowest expression levels of NPY1R mRNA, for example, were those with the most extreme AT (Roseboom et al., 2013). NYP1R is of interest because of the numerous reports linking decreased NPY system activity to depression. While Ce NYP1R mRNA levels did not predict Ce metabolism, a whole-brain voxelwise analysis revealed several other regions where Ce NYP1R mRNA expression did predict metabolism. These regions included the dorsolateral prefrontal cortex (dlPFC) and perigenual anterior cingulate cortex, cortical regions known to be part of the circuit that regulates amygdalar activity (Davidson, 2002; Etkin et al., 2006; Buhle et al., 2013; Shackman et al., 2013). These data suggest that NPY1R mRNA levels in the Ce may be regulated by prefrontal cortical inputs to NPY1R-expressing Ce neurons. Alternatively, NPY1R-expressing Ce neurons could modulate metabolism in these distal brain regions via direct or indirect mechanisms.

**Living without an amygdala**

Lesion studies in human and non-human primates suggest a causal role for the amygdala in AT. Initial studies by Brown & Schafer demonstrated decreased fearfulness in monkeys with amygdala damage (Brown and Schafer, 1888). Specific experimental lesions to the amygdala have been shown to decrease the reticence to act in potentially threatening situations (Kalin et al., 2001; Murray and Izquierdo, 2007; Machado and Bachevalier, 2008; Chudasama et al., 2009) and alter stress-induced cortisol release (Machado and Bachevalier, 2008). Importantly, amygdala lesions also resulted in less anxiety in social situations where human AT is most commonly observed (Emery et al., 2001; Machado et al., 2008). We note that other studies have used the human intruder paradigm to assess the effects of amygdala lesions on behavior; these studies are reviewed in other chapters in this volume. Also reviewed elsewhere in this volume are the seminal studies of patient S.M., a woman with calcification of the amygdala as a result of

Urbach-Wiethe disease. Years of clinical and experimental assessment have found that S.M. is more trusting of and more likely to approach strangers (Adolphs et al., 1998), does not recognize fear in others (Adolphs et al., 1994), shows a "blindness" for socially acceptable physical space (Kennedy et al., 2009), does not readily learn novel Pavlovian fear associations (Bechara et al., 1995), and does not show typical signs of anxiety (Feinstein et al., 2011). Taken together, these data suggest that SM displays less anxiety in social and other threatening situations, and fit with data from adult rhesus monkeys with amygdalar lesions that display altered social behavior (Emery et al., 2001; Amaral, 2002; Machado et al., 2008). See also (Terburg et al., 2012), and Chapter 12 in this volume, for a different interpretation of the deficits associated with human amygdala lesions resulting from Urbach-Wiethe disease.

In an initial study aimed at understanding the role of amygdala in monkey AT, we lesioned the entire amygdala with the neurotoxin ibotenic acid (Kalin et al., 2001). Lesioned animals displayed less fear-related behavior in the presence of a live snake or novel adult conspecific. However, no reduction in freezing behavior was observed in response to the human intruder. In hindsight, we believe that this null result reflects an unintended consequence of the fact that the lesioned monkeys in this study were repeatedly exposed to the human intruder paradigm prior to surgery. Other work by our group (Fox et al., 2012) indicates that although individual differences in freezing are moderately stable, absolute levels of freezing tend to decrease with repeated exposure to the human intruder paradigm. Thus, it is possible that the apparent lack of effect of the lesions on freezing in this experiment was due to repeated exposure associated habituation.

Alterations in sleep were also observed in the monkeys with large amygdala lesions (Benca et al., 2000). Specifically, lesioned and control monkeys were adapted to EEG recording during their nocturnal sleep period. Despite apparent adaptation, the sleep patterns of control animals were punctuated by frequent arousals. Monkeys with large bilateral lesions of the amygdala had more sleep and a higher proportion of REM sleep compared to control animals, suggesting that the amygdala may be important in mediating the effects of stress on sleep. This is interesting considering that anxiety is the psychiatric symptom most often associated with insomnia, and the growing recognition of that sleep disturbances accompany almost all forms of psychopathology (Benca et al., 1992).

In a follow-up lesion study we focused more specifically on the Ce. In that study, the monkeys were intentionally kept naïve to the human intruder paradigm and were exposed to it

only once, following recovery from the lesion surgery (Kalin et al., 2004). Small selective lesions in the Ce region were produced to examine the extent to which the Ce mediates unconditioned fear, AT-related behavioral responses, and stress-induced pituitary-adrenal activity (Figure 7). There were two experimental groups [bilateral lesion (n=9) and unilateral (n=5) Ce lesions) and an age-matched unoperated control group (n=16).

[insert Figure 7 here]

The Ce lesions significantly affected coo vocalizations and freezing duration, the two behavioral components of AT. Compared with the age-matched controls, cooing was increased in the bilateral-lesion and unilateral-lesion groups ($p < 0.04$). The bilateral-lesion group showed significantly less freezing behavior compared to the other groups ($p < 0.023$). The bilateral lesioned animals also displayed less fear when exposed to a live snake, suggesting that these effects generalize beyond the human intruder paradigm. Decreases in adrenocorticotropin releasing hormone (ACTH) and cerebrospinal fluid levels of corticotropin releasing hormone (CRH), the two key upstream mediators of cortisol release were observed, and individual differences in the extent of the lesion significantly predicted stress-related cortisol levels (Kalin et al., 2004). In conjunction with the FDG imaging results, these findings indicate a mechanistic role for the Ce in mediating the behavioral and pituitary-adrenal components of AT, as well as other fear-related behaviors, early in life.

**Cortical and subcortical systems interacting with Ce in relation to AT**

Psychiatric disorders likely reflect alterations in the coordinated activity of distributed functional circuits. While the results of our FDG and lesion studies suggest that the Ce is a key substrate for stable individual differences in AT, they do not directly address the larger functional network in which the Ce is embedded. To understand the long-range neural networks that may interact with the Ce in relation to AT, we used fMRI to assess functional connectivity of the Ce region. Based on work demonstrating the ability to reliably assess functional connectivity in anesthetized rhesus monkeys (Vincent et al., 2007), we used the Ce as a seed region to examine temporal correlations of the BOLD signal in a subset of the monkeys from the large-sample described above (Oler et al., 2010). By combining data from multiple modalities (FDG-PET and fMRI) we found that greater Ce glucose metabolism was associated with decreased

functional coupling between the Ce and dlPFC, and that decreased functional coupling between the Ce and dlPFC was also associated with higher levels of AT (Birn et al., 2014). Decreased Ce-dlPFC connectivity was also observed in a sample of pre-adolescent children (ages 8-12) with anxiety disorders, further validating the monkey AT model, suggesting a role for altered dlPFC-amygdala functional coupling in the pathogenesis of childhood anxiety disorders and demonstrating that the modulatory influence of dlPFC on amygdala function is evolutionarily conserved (Birn et al., 2014). Importantly, the monkey FDG-PET data provided evidence that elevated Ce metabolism statistically mediates the association between Ce-dlPFC connectivity and elevated AT (Birn et al., 2014). Thus, these functional connectivity data suggest that coordinated activity between dlPFC and Ce is an important modulator of individual differences in the expression of AT. This highlights an important benefit of assessing functional connectivity, as findings are not constrained by direct neuroanatomical connections. Future studies aimed at directly modulating dlPFC-Ce functional connectivity would help in further understanding the role of dlPFC in regulating amygdala function and AT as well as in children with anxiety disorders. In this regard, transcranial magnetic stimulation is a noninvasive strategy that could be used in both human and non-human primates to stimulate the dlPFC and examine downstream effects on amygdala function as well as on affecting dlPFC-amygdala connectivity.

In addition to the amygdala, FDG-PET imaging studies suggest that AT reflects individual differences in a number of regions that include the anterior hippocampus, BST, anterior temporal cortex and PAG. The caudal orbitofrontal cortex (OFC) also appears to play a role (FDR $q<.05$, corrected; unpublished analyses of the n=238 sample described by Oler et al 2010). Furthermore, aspiration lesions of the OFC reduce freezing in response to the NEC challenge (Kalin et al., 2007). Importantly, whole-brain FDG-PET imaging provided evidence suggesting that the reduction in freezing observed in OFC-lesioned animals reflects an indirect consequence of lesion-induced alterations in the extended amygdala. Specifically, OFC lesions reduced NEC-related metabolism in the BST (Fox et al., 2010). It is important to emphasize that while OFC lesions attenuate freezing and decrease BST metabolism, the correlation between BST activity and freezing behavior, evident prior to the lesions, remained significant after the lesions (Fox et al., 2010). This suggests that decreased freezing behavior in OFC lesioned animals was directly related to decreased activity in the BST, and supports previously reported findings that individual differences in BST metabolic activity are predictive of individual differences in freezing and/or AT in young monkeys (Kalin et al., 2005; Fox et al., 2008). Thus, future studies

examining the mechanistic role of BST in primate anxiety should employ selective BST lesion techniques similar to those described above, and in other chapters in this volume, to dissociate the selective role that this component of the extended amygdala may play in normal and pathological anxiety.

**Concluding Remarks and Future Directions**

The functional neuroimaging data in intact animals and behavioral data from Ce-lesioned animals reviewed above extend prior studies on the function of the Ce. First, we demonstrated a mechanistic role for the Ce in the behavioral and pituitary-adrenal components of AT using selective ibotenic acid lesions. Then, building on earlier studies, we demonstrated that Ce metabolism strongly predicts individual differences in AT. In this large sample, we demonstrated that polymorphisms in the CRH receptor system are associated with heightened anxiety and elevated metabolic activity in the Ce in response to potential threat. In a subsample, we found that mRNA expression of neurodevelopment-related genes is decreased in the Ce of anxious monkeys, which suggests that learning-related neuroplasticity phenomena in the amygdala may be compromised in individuals with extreme anxious phenotypes. Additionally, we uncovered evidence suggesting that dorsolateral and orbital regions of the PFC influence AT-related activity within the extended amygdala. Taken together, these data indicate a role for a circuit centered on the extended amygdala, encompassing the Ce and BST, in the establishing and maintaining normative and extreme anxiety early in life.

Future studies employing lesion or reversible inactivation techniques that target specific neuronal sub-populations will likely deepen our understanding of the amygdalar microcircuits that underlie primate AT. Furthermore, rapid immunohistochemical staining to identify specific cell populations for micro-dissection and subsequent deep RNA sequencing is a promising method for understanding the cell-specific molecular mechanisms related to AT. Gene delivery with viral vectors to induce or suppress expression of specific molecules is another technique with the potential to enrich our understanding of primate amygdalar microcircuit function and the role of the extended amygdala in temperamental anxiety. With the ultimate aim of developing more effective early-life interventions to treat and prevent anxiety-related psychopathology, it is our hope that such studies will shed light on the risk for anxiety-related psychopathology as well as deepen our understanding of amygdala function and normal variation in temperament.

Table 1. Parallels between monkey anxious temperament (AT) and childhood behavioral inhibition (BI).

| Phenotypic features | AT in Juvenile Monkeys | BI in Children |
|---|---|---|
| Increased freezing/reduced motor activity/passive avoidance in the presence of adult strangers | **YES** (Kalin and Shelton, 1989; Kalin et al., 1998; Fox et al., 2008; Oler et al., 2010; Fox et al., 2012; Shackman et al., 2013) | **YES** (Fox et al., 2005; Hirshfeld-Becker et al., 2008; Degnan et al., 2010) |
| Less frequent vocal communication | **YES** (Kalin and Shelton, 1989; Fox et al., 2008; Oler et al., 2010; Fox et al., 2012; Shackman et al., 2013) | **YES** (Fox et al., 2005; Hirshfeld-Becker et al., 2008; Degnan et al., 2010) |
| Moderate stability across time and context | **YES** (Fox et al., 2008; Fox et al., 2012; Shackman et al., 2013) | **YES** (Pfeifer et al., 2002; Fox et al., 2005; Hirshfeld-Becker et al., 2008; Degnan et al., 2010; Brooker et al., 2013) |
| Significant functional impairment or distress | ***Unknown*** | **Variable** (Fox et al., 2005; Hirshfeld-Becker et al., 2008; Degnan et al., 2010) |
| Heritable | **YES** (Williamson et al., 2003; Oler et al., 2010) | **YES** (Rickman and Davidson, 1994; Hirshfeld-Becker et al., 2008) |
| Reduced by anxiolytic administration | **YES** (Kalin and Shelton, 1989; Davidson et al., 1992; Davidson et al., 1993) | ***Unknown*** |
| Increased pituitary-adrenal activity (cortisol) | **Not consistently observed** (Kalin et al., 1998; Fox et al., 2008; Oler et al., 2010; Fox et al., 2012; Shackman et al., 2013) | **Not consistently observed** (Schmidt et al., 1997; de Haan et al., 1998; Fox et al., 2005) |
| Right-lateralized frontal EEG activity | **YES** (Davidson et al., 1993; Kalin et al., 1998) | **YES** (Davidson and Rickman, 1999; Buss et al., 2003; Fox et al., 2005) |
| Increased or sustained amygdala activity to novelty and potential threat | **YES** (Fox et al., 2008; Oler et al., 2010; Fox et al., 2012; Shackman et al., 2013) | **YES (some data are from retrospective studies in adults)** (Schwartz et al., 2003; Blackford et al., 2011) |
| Altered functional connectivity between the amygdala and prefrontal cortex | **YES** (Birn et al., 2014) | **YES** (Hardee et al., 2013) |

Figure 1

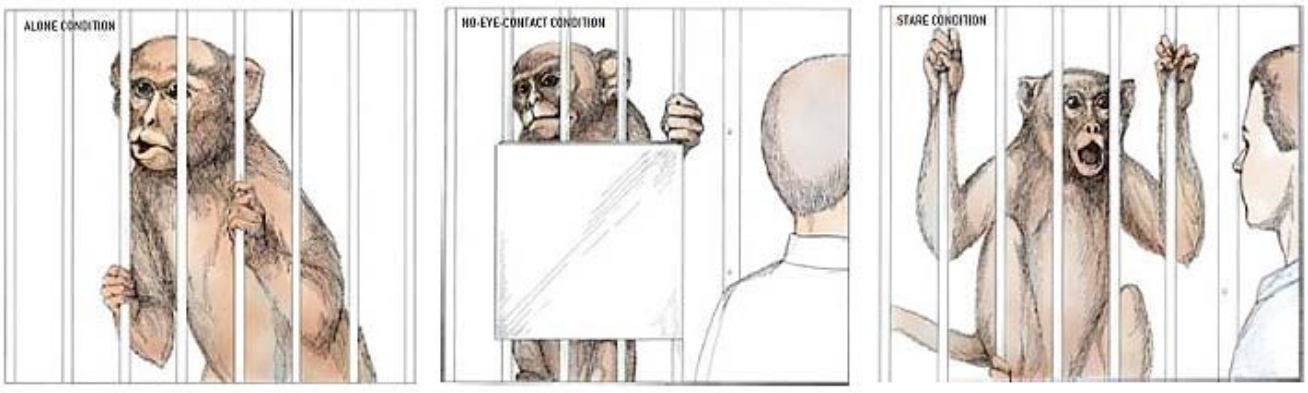


Figure 1. The three experimental conditions of the human intruder paradigm elicit distinct fear-related behaviors in young rhesus monkeys. When alone and separated from their cagemate (left), young monkeys actively explore the test cage and spontaneously emit "coo" calls, thought to reflect an attempt to attract help from their mothers or other conspecifics. In the next condition a human intruder presents his or her profile while avoiding direct eye contact with the monkey (NEC, center). In this situation the monkeys typically orient their focus on the intruder, trying to evade discovery by remaining completely still (freezing) or hiding behind their food bin (opaque box in the center panel). In the third condition, the human intruder enters the room and stares at the animal (right). This direct threat condition often elicits aggressive behaviors (e.g., barking, threatening gestures, cage rattling). This figure was reprinted with permission (Kalin, 1997).

Figure 2

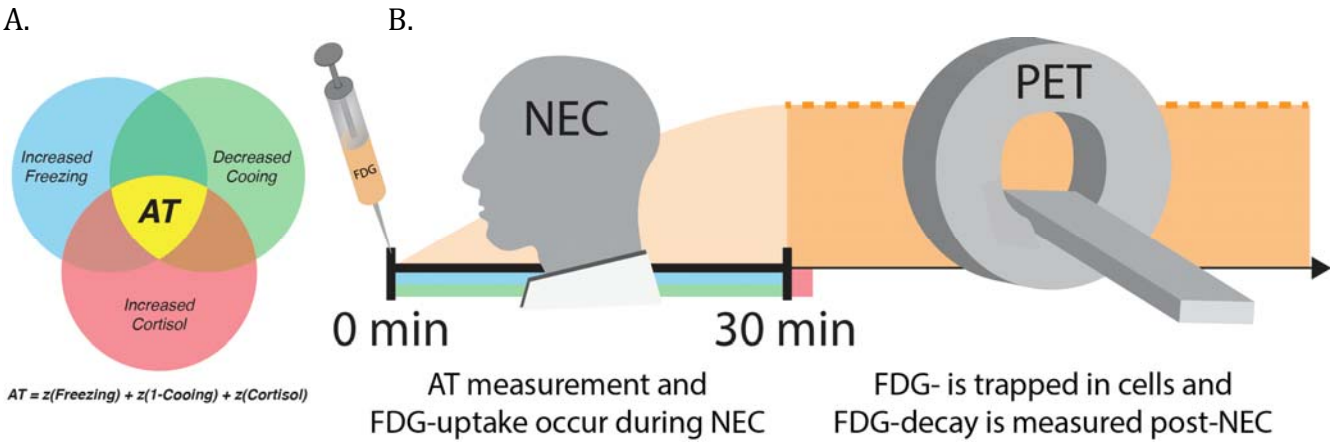


Figure 2. (A) AT is calculated as the mean z-scores of NEC-induced freezing, coo vocalizations [reverse-scored], and plasma cortisol levels. (B) To measure NEC-induced regional brain metabolism, monkeys were injected with a radiotracer (18-FDG) immediately prior to exposure of the 30-min NEC challenge depicted in Figure 1. Following NEC exposure the monkeys were anesthetized, blood was collected for cortisol, and the animals were placed in a high-resolution microPET scanner to measure FDG uptake, integrated across the 30-min NEC challenge.

Figure 3

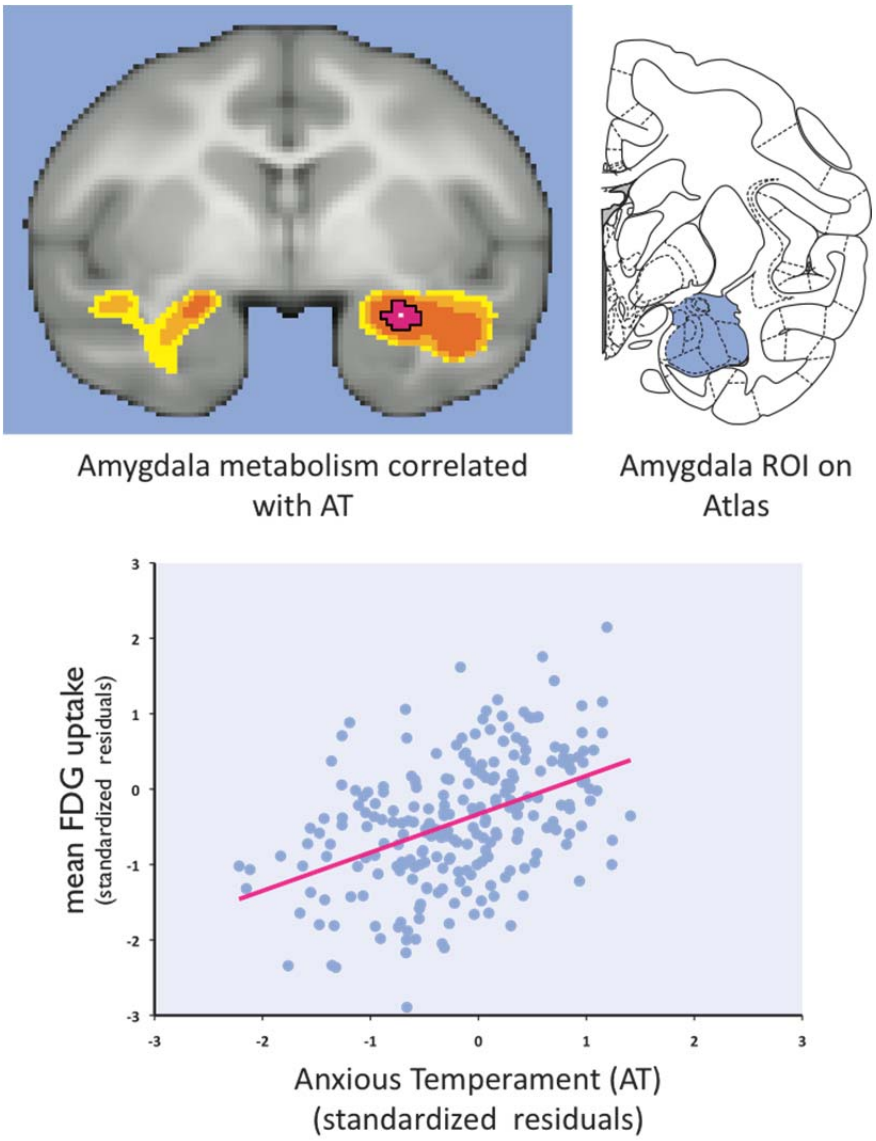


Figure 3. To understand the relation between individual differences in regional brain metabolism and AT, whole-brain voxelwise regression analysis was performed in 238 young monkeys while controlling for nuisance effects of age, sex and voxelwise gray-matter probability. Results revealed a peak FDG-AT correlation in the region of the Ce (significance of correlations: yellow, $p<0.05$; light orange, $p<0.01$; dark orange, $P<0.001$, adjusted for multiple comparisons using the Šidák correction.) The area in pink represents the 95% spatial confidence interval of the peak FDG-AT correlation in the amygdala. This figure was adapted with permission from Oler et al., 2010).

Figure 4

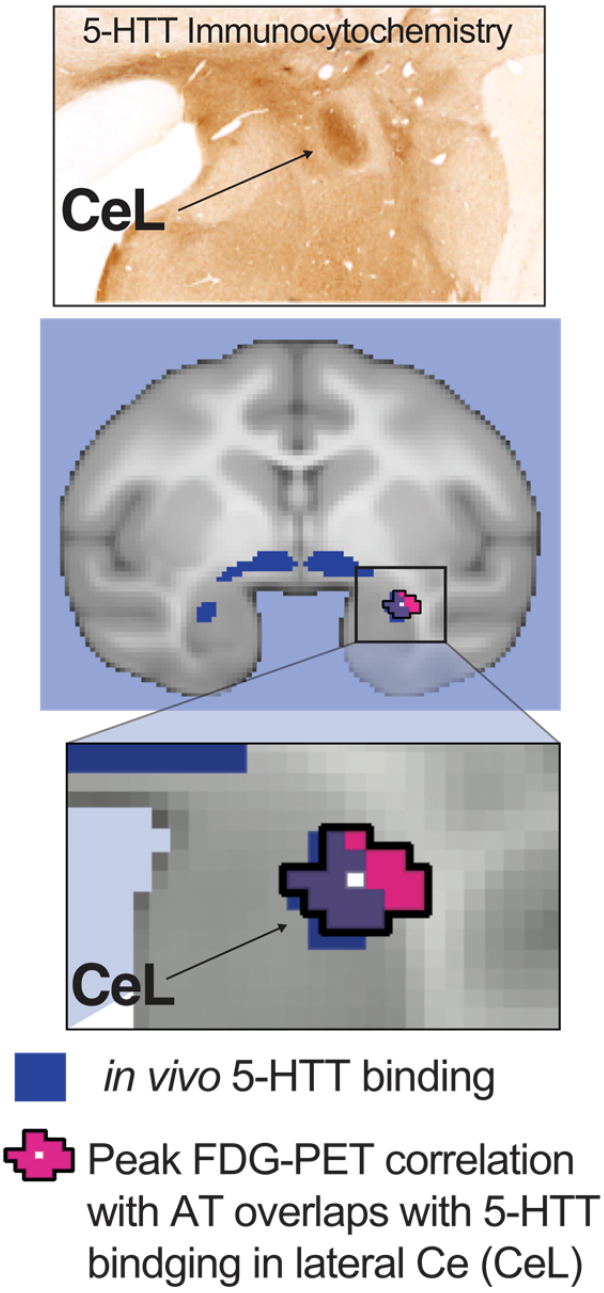


Figure 4. *In vivo* serotonin transporter (5-HTT) binding localized the dorsal amygdala cluster to the Ce. (**Top**) A low-power photomicrograph of *ex vivo* 5-HTT immunohistochemistry showing substantial immunoreactivity in the lateral division of Ce [adapted with permission from O'Rourke and Fudge (2006) Copyright Elsevier]. High levels of 5-HTT are a chemoarchitectonic hallmark of the lateral subdivision of the Ce (CeL). (**Middle**) Overlap between the amygdala 95% spatial confidence interval of the peak FDG-AT correlation (pink) and *in vivo* 5-HTT availability (dark blue = 250X background 5-HTT binding). High 5-HTT availability was also observed within the substantia innominata, which can be seen just below the anterior commissure, medial and dorsal to the Ce and in the region of the dorsal raphe nucleus (not shown). (**Bottom**) Magnified coronal view of the overlap between 5-HTT binding and the FDG-PET correlation as shown in the middle panel.

Figure 5

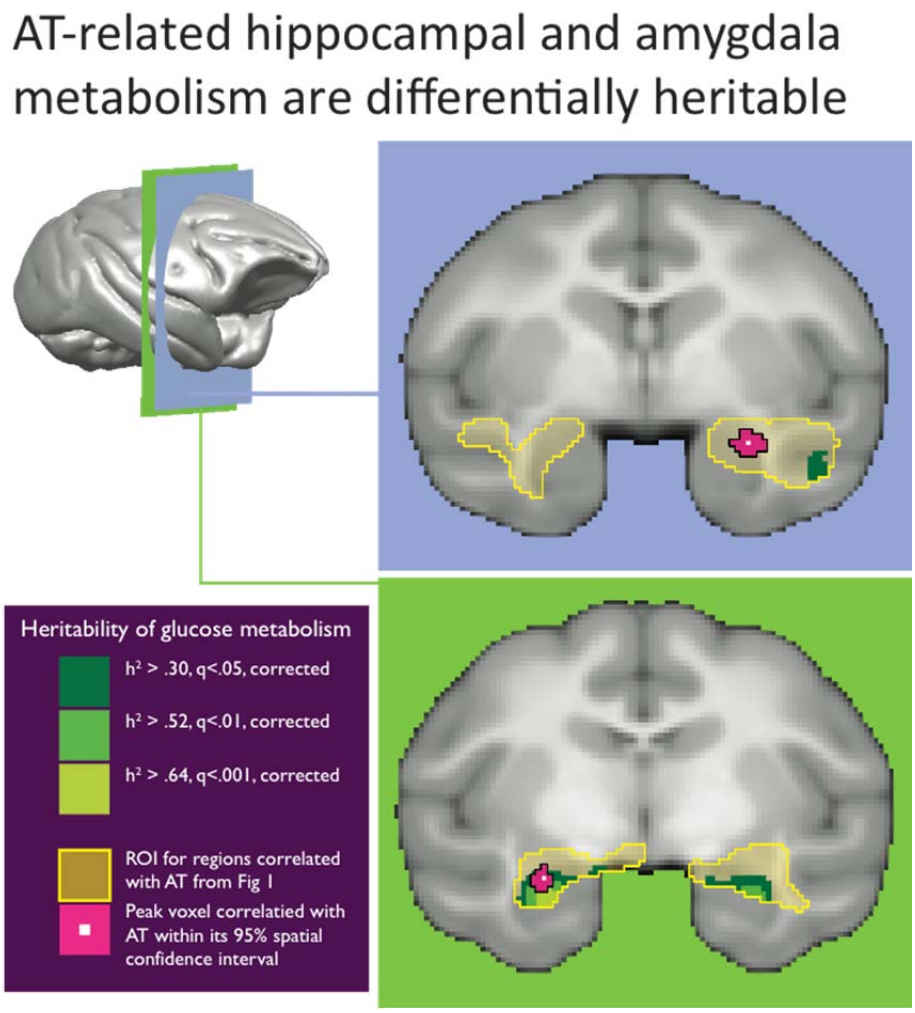


Figure 5. Overlap between regional metabolic activity predictive of AT (yellow) and regions that are significantly heritable. No significantly heritable voxels were observed in the dorsal amygdala region (**top**), although within the same slice significant heritability was detected in the superior temporal sulcus. (**Bottom**), Glucose metabolism was significantly heritable in both the right and left anterior hippocampus, where it overlaps with the left anterior hippocampal region that correlated with AT (yellow, regions predictive of AT; dark green to light green, false discovery rate: q=0.05, q=0.01, q=0.001). This figure was adapted with permission from Oler et al., (2010).

Figure 6

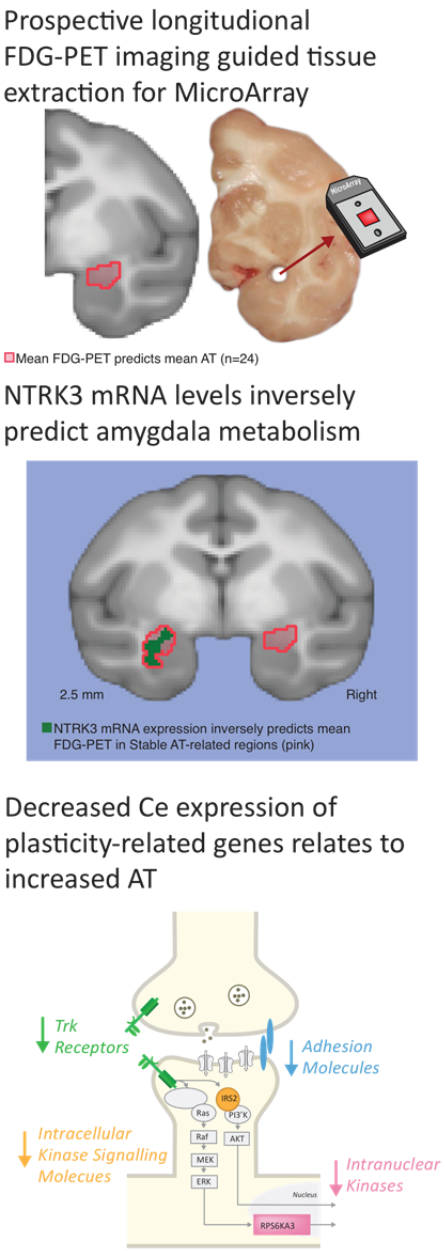


Figure 6. Microarray data demonstrated that individuals with higher levels of Ce NTRK3 mRNA expression exhibited lower AT. (**Top**) Ce regions predictive of dispositional AT were used to guide amygdala biopsy for analysis of AT-related RNA expression. A slice through the functionally defined amygdala region juxtaposed with a representative single-subject slab in which the dorsal amygdala was biopsied. (**Middle**) NTRK3 expression negatively predicts Ce metabolism. Individuals showing higher levels of NTRK3 mRNA expression, indexed by qRT-PCR, show reduced Ce metabolism *in vivo* (green) [FDR-corrected within the stable AT-related region (pink)]. (**Bottom**) Portrayal of the neuroplasticity-associated, NTRK3 (Trk receptor, green) pathway. A similar pattern in relation to AT was found for IRS2 (orange) and RPS6KA3 (pink), two downstream targets of NTRK3. Other molecules in the NTRK3 pathway are depicted in gray. Figure was adapted from Fox et al., (2012) and reprinted with permission.

Figure 7

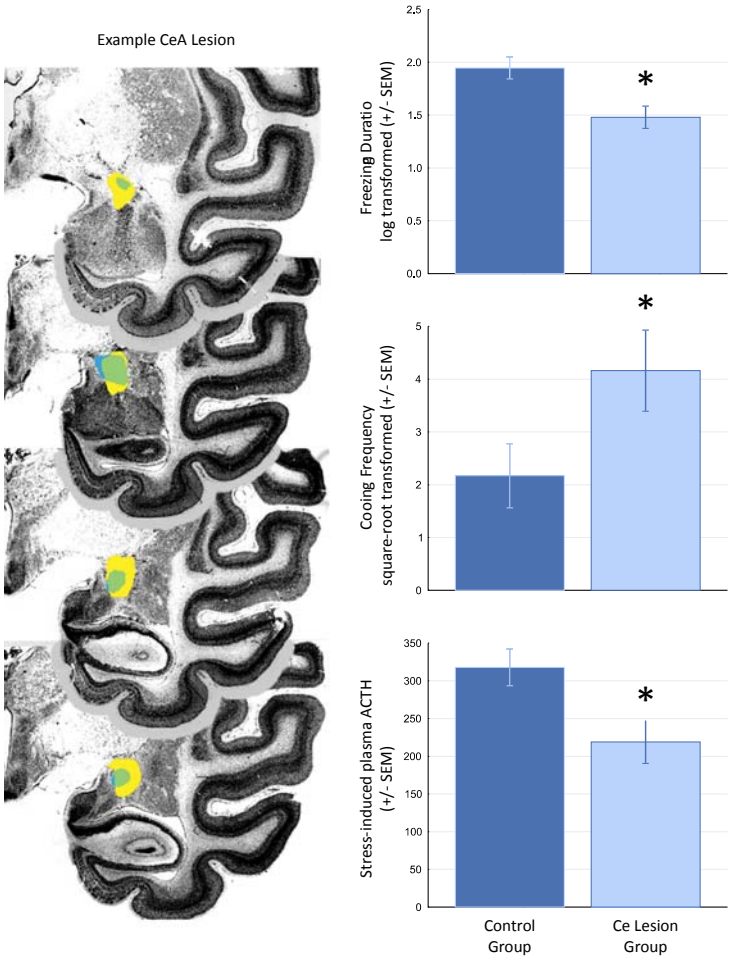


Figure 7. The effects of Ce lesions on components of AT. **Left**, a representative lesion is displayed on four coronal sections through the anterior – posterior (top to bottom) extent of Ce. The intact Ce is depicted in blue, the area of the total lesion is displayed in yellow, and the Ce region that is lesioned is depicted by the overlap in green. **Right**, monkeys with Ce lesions displayed less freezing (top), emitted more coo calls (middle), and released less ACTH (bottom) during exposure to the human intruder paradigm. Figure modified from Kalin et al., (2004) and reprinted with permission.

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